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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/241,347	02/02/1999	HERMANN BUJARD	BBI-009C4CN	8608

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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 05/21/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/241,347

Applicant(s)

BUJARD ET AL.

Examiner

Ram R. Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,5,7-11,13-16,18,19 and 21-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,5,7-11,13-16,18,19 and 21-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1, 2, 4, 5, 7-11, 13-16, 18, 19 and 21-28 drawn to a non-human transgenic animal in Paper No. 18 is acknowledged.
2. Claim 12 has been cancelled.
3. Applicants' response filed 8-14-02 has been received and entered.
4. Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19 and 21-28 are under consideration.

Information Disclosure Statement

5. Regarding the IDS, applicants have argued that the IDS filed on 12-13-99 is a copy of the IDS filed 8-23-99. However, no IDS filed on 8-23-99 could be located in the application. Applications are required to file a copy of the letter and receipt indicating the filing of the IDS on 8-23-99 and copies of the articles.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19 and 21-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse, whose genome comprises: a first transgene comprising a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein that inhibits transcription in eukaryotic cells wherein the fusion protein comprises a tet repressor or mutated tet repressor that binds to a tet operator in the absence or presence of tetracycline or tetracycline analog and that is operatively linked to a heterologous polypeptide which inhibits transcription in eukaryotic cells and a second transgene comprising a

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gene of interest operatively linked to at least one tet operator sequence, wherein said gene of interest confers a detectable and functional phenotype on the mouse when expressed in cells of the mouse, wherein the level of expression of the tet-operator linked gene of interest can be upregulated by administering tetracycline or tetracycline analogue to the mouse and a method for modulating transcription of the second transgene in the transgenic animal by administering tetracycline or tetracycline analog to the animal, does not reasonably provide enablement for any other embodiment, for reasons of record set forth in the previous office action of 7-8-99 and 9-13-01 and as discussed below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments

Applicant's arguments filed 12-13-99 have been fully considered but they are not persuasive. In the pages 7 and 8 applicants reiterate their invention as recited in claims. In the last paragraph on page 8, applicants list references in support of their argument that the specification is enabled. However, as noted in the previous office actions, in view of the unpredictability of the art as evidenced by the arts used in the previous office actions, these arts do not address the issues raised in the previous office action. Regarding the issue of the arts in which the inventors share authorship with Weinmann et al, it is noted that Weinmann et al article is in plant and that is not an invention under consideration here. Likewise the arguments regarding, transgenic organisms are not relevant since the claimed invention is to transgenic non-human animals. Applicants argue that since the construct works in *Drosophila*, *Xenopus*, mice, sea urchins and plants, it would be expected it will work in other organisms. However, these arguments do not address the issues of the unpredictability of making transgenic animals and what will be their characteristics and in the absence of the unpredictability of the characteristics and phenotypes, how will an artisan use the transgenic animals recited. Applicants arguments that

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Hammer et al does not teach phenotypic difference due to differential activity is not persuasive because Hammer teaches the unpredictability of getting the same phenotypes and characteristics in transgenic mice and rat using the same transgene which shows that it is unpredictable whether using the same construct animals of different species can be created and that have same characteristics and phenotypes. Applicants have argued and cited Amgen Inc v. Chugai Pharmaceuticals case in support of their arguments, however, they have ignored the fact that in an unpredictable art more is required in the specification. Applicants' attention is drawn to MPEP 2164.03, which discusses "Relationship of Predictability of the Art and the Enablement"

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification.

In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling."

In summary, applicants' arguments are not sufficient to address all the enablement issues raised in the previous office action and therefore, the scope of the enablement rejection is maintained as discussed above.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.3218 may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-11 and 13-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5, 866,755 (2-2-1999), for reasons of record set forth in the previous office action of 7-8-99.

Applicants' response that a terminal disclaimer would be filled upon agreement and acceptance of the claims in the application is acknowledged.

10. Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19 and 21-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to transgenic non-human animals and methods of using such wherein a transgene (integrated in the genome of the transgenic animals) encodes a fusion protein comprising a Tet repressor and a transcription silencer

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domain of a protein (selected from a group of proteins) and the fusion protein binds to a tet operator sequence (operably linked to an exogenous gene) in the presence or absence of tetracycline or a tetracycline analog. Another limitation of the invention recites that the transgene is integrated to a predetermined location within a chromosome within the cells of the animals.

The specification teaches making and using of a transgenic mouse that has integrated first transgene encoding a fusion protein comprising the sequence encoding the tet repressor protein (that binds to tet operator) operatively linked to the transcription silencer domain of a protein selected from a list (given earlier) and a method for modulating the expression of a gene of interest (that is also integrated in the genome of the transgenic mouse) by administering tetracyclin or tetracyclin analog.

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention encompasses an transgenic animal of any species. Considering the fact that the claimed invention encompass transgenic animals of any species, the phenotype(s) of the claimed animals can not be predicted because the art of making transgenic animals or knockout animals is highly unpredictable. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find

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the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype".

This clearly indicates that the phenotype of a transgenic mouse or rat or any animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics and in view of the unpredictability of getting same phenotype in different species of animals using the transgene, it can be predicted as to what will the identifying characteristics of the transgenic animals of different animals species, whether they will have the same characteristics or different characteristics or what characteristics. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the transgenic mice disclosed.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

1. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. The after-final fax number is (703) 87209307. Any inquiry of a general nature, formal

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matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.



RAM SHUKLA
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632